Ann. Hum. Genet., Lond. (1970), **33**, 227
Printed in Great Britain

Achondroplasia—a genetic and statistical survey

By J. L. MURDOCH, B. A. WALKER, J. G. HALL, H. ABBEY, K. K. SMITH and V. A. McKUSICK

The Division of Medical Genetics, Department of Medicine, and the Department of Biostatistics, Johns Hopkins University, Baltimore, Maryland 21205

INTRODUCTION

Achondroplasia is the commonest form of skeletal dysplasia leading to dwarfism. The clinical features of short stature, large head, long trunk and stubby limbs are familiar to all. The designation *achondroplasia* was proposed by Parrot in 1878, although he was not the first to distinguish this disorder from rickets.

Estimates of the frequency of achondroplasia differ widely. Mørch (1941) found that in Denmark there was approximately one case in every 10,000 livebirths. Of these he believed 80% died within the first year of life giving a frequency of 20 per million in the general population of Denmark. As pointed out by Slatis (1955), this estimate is probably high as there is some confusion regarding the diagnostic criteria used and there appear to have been some recessive disorders and individuals with spondylo-epiphyseal dysplasia included (Silverman & Brunner, 1967). The incidence in the U.S. has been estimated to be 15 per million (Potter & Coverstone, 1948) and in Northern Ireland 28 per million (Stevenson, 1957).

The primary defect in achondroplasia is unknown but is thought to result in inhibition of interstitial chondroblastic activity in the growth plate (Rubin, 1964). Only endochondral bone is involved, membranous bone formation continuing in the normal manner. Thus in the skull, the endochondral bone of the base is severely affected while the membranous bone of the vault is relatively uninvolved. This leads to the characteristic appearance of high forehead with frontal bossing and 'scooped out' face.

The dwarfism is of the short-limbed variety and of rhizomelic type; that is, the upper arms and legs are shortened comparatively more than the distal segments. The spine is lordotic and the sacral tilt leads to prominence of the buttocks. This tilt, accompanied by the flat-roofed acetabula and the bowed legs leads to a duck-like walk. Although the hands are short and stubby, they appear large in comparison to the more abbreviated limbs. There is a characteristic space between the third and fourth digits which, together with the wide proximal phalanges, leads to difficulty in opposing the fingers, giving the characteristic three-pronged hand, the *main en trident* of Marie (1900).

A new mutation is thought to be the cause of over 80% of cases, less than 20% being familial. Those achondroplasics who survive the first year of life have comparatively good health, although about half are thought to have self-limiting hydrocephalus in infancy. This may be due both to the small foramen magnum and to true megencephaly which is found as a non-skeletal effect of the achondroplasia gene (Dennis, Rosenberg & Alvord, 1961). The narrowed spinal canal enclosing a relatively normal spinal cord predisposes to neurological disorders caused by compression of the cord and nerve roots by osteophytes, prolapsed intervertebral discs, or deformity of the vertebral bodies (Vogl, 1962).

Reproductive fitness is considerably reduced, in part because of social difficulties in finding a mate and in part because of obstetric problems created by the small pelvis.

The radiologic changes include a shortened skull base with small foramen magnum and large vault. The interpedicular distance diminishes progressively from the thoracic vertebrae to the sacrum, which is the reverse of the normal finding. The long bones are rectangular with slight outward bowing and there may be V-shaped growth plates. An important radiologic sign is the narrow and relatively deep greater sciatic notch in a flat pelvis (Langer, Baumann & Gorlin, 1967).

PURPOSE OF PRESENT STUDY

Although this common form of short stature is easily recognized clinically and radiologically in the individual case, there remain questions that can only be answered if a large number of affected persons is studied.

It is the purpose of this paper to compile specific data that will be of value in counselling achondroplasics and their parents.

The Little People of America, Inc. (LPA), an organization formed in 1960 and open to individuals under 58 in. in height, provided an excellent opportunity to gather information on a series of achondroplasics. In co-operation with LPA, those attending national and district meetings of the organization were given opportunity to talk to a physician and fill in a questionnaire.

The diagnosis of achondroplasic dwarfism was made by members of the medical genetics staff and in many cases was confirmed by appropriate radiologic studies.

Information was available on 148 affected individuals, of whom 117 (58 males and 59 females) were sporadic cases with no parental history of dwarfism. The remaining 31 (15 males and 16 females) were familial cases with one or both parents affected.

An attempt was made to evaluate these groups separately and to obtain the following information:

On the sporadic cases: (1) Birth weight and length; (2) adult weight and height; (3) correlation of adult height with parental height; (4) parental age at the birth of the affected individual (*a*) compared with the age at the birth of the normal sibs, and (*b*) compared with that in the general population; (5) birth order; (6) ethnic background; (7) marriage; (8) reproductive performance.

On the familial cases: (1) birth weight and length; (2) adult weight and height; (3) number and health of sibs; (4) marriage; (5) reproductive performance.

RESULTS

A summary of the information obtained on 148 achondroplasic dwarfs is presented in Appendices 1 and 2.

Birth weights and lengths

These measurements were tabulated separately for individuals with normal mothers and those with dwarfed mothers because of the frequency of premature and Caesarian deliveries in dwarfed women. The group with normal mothers contained all sporadic cases and those familial cases with normal mothers. The remainder of the familial cases had dwarfed mothers who had achondroplasia or another skeletal dysplasia.

Birth weights

Achondroplasics with normal mothers: 45 males, mean weight 7·69 lb., S.D. 1·36; 48 females, mean weight 6·90 lb., S.D. 1·28.

Achondroplasics with dwarfed mothers: 11 males, mean weight 6·51 lb., S.D. 0·58; 11 females, mean weight 5·99 lb., S.D. 1·15.

There were fewer birth lengths known but they were divided in a similar manner.

Birth lengths

Achondroplasics with normal mothers: 31 males, mean length 18·84 in., S.D. 1·36; 32 females, mean length 18·55 in., S.D. 1·01.

Achondroplasics with dwarfed mothers: 11 males, mean length 17·95 in., S.D. 0·46; 8 females, mean length 18·00 in., S.D. 1·60.

Adult heights and weights

These measurements were tabulated on all achondroplasics on whom both values were available. Achondroplasics 16 years of age or older were included whether sporadic or familial cases.

	Mean adult height (in.)		Mean adult weight (lb.)	
51 males	51·81	S.D. 2·22	120·61	S.D. 29·61
55 females	48·62	S.D. 2·37	100·62	S.D. 17·51
All 106 individuals	50·16	S.D. 2·79	110·24	S.D. 26·00

Adult height correlated with parental height

The heights of both the mother and father were reported for 84 of the adult sporadic cases. This group was composed of 41 males and 43 females and the adult height of the achondroplasic was plotted against (1) paternal height, (2) maternal height, and (3) mean parental height. No relationship was apparent.

Linear correlation coefficients were also calculated as follows.

(1) (*a*) Male achondroplasics: adult height *v.* paternal height; correlation coefficient = +0·02; (*b*) female achondroplasics: adult height *v.* paternal height = +0·20.

(2) (*a*) Male achondroplasics: height *v.* maternal height = +0·01; (*b*) female achondroplasics: height *v.* maternal height = +0·08.

(3) (*a*) Male achondroplasics: height *v.* mean parental height = +0·02; (*b*) female achondroplasics: height *v.* mean parental height = +0·18.

Table 1. *Mean ages of mothers by birth order*

Birth order	All mothers, 1955 U.S. (mean age)	Mothers of achondroplasics	
		Mean age	No.
1	22·63	24·66	(18)
2	25·51	28·42	(26)
3	27·92	31·13	(24)
4	29·59	32·89	(9)
5	30·94	34·57	(7)
6	32·11	32·50	(8)
7	33·28	38·00	(3)
8	34·45	38·33	(3)
9	35·20	37·00	(3)
10	36·56	41·00	(1)
13	39·01	40·00	(1)

These linear correlation coefficients show that there is little or no association between the height of the parents and the final adult height of achondroplasics with the possible exception of the paternal height for female achondroplasics.

Parental age and birth order

The mean parental ages at the birth of a sporadic achondroplasic infant were: fathers, 36·08 years, S.D. 7·65 (106 fathers); mothers, 30·52 years, S.D. 5·91 (106 mothers).

The control means from Table 3 are: fathers, 29·85 years; mothers, 26·54 years.

The mean parental ages for achondroplasics are thus 6·2 years in excess of the controls for fathers and 4·0 years for mothers.

The mean birth order for the achondroplasic infant was 3·48, S.D. 2·35. The control from Table 6 was 2·64, S.D. 1·93.

In an attempt to separate the maternal and paternal components of the parental age effect three approaches were used.

The first used a comparison of the mean age of the mothers of achondroplasics with the mean of mothers from the general population matched for the birth order of their children. Table 1 is a comparison of these means for different birth orders.

For the 103 mothers of achondroplasics the mean age was 30·57 years, S.D. 5·93. The mean age of mothers from the general population matched for birth order was 27·81 years, S.D. 5·93.

This matching by birth order reduced the age excess of the mothers of achondroplasics from 4·0 years, when all mothers were used as controls, to 2·8 years. However, this is still significant whether the t test ($P = 0{\cdot}001$) or sign test (1 % level) is used.

Unfortunately similar figures are not available for fathers' age *v.* birth order, so it is impossible to decide from these data if this maternal age effect is a significant factor in causing new mutations or only a reflexion of the paternal age effect as older fathers tend to be married to older mothers.

The second method used in an attempt to evaluate the parental age effect was that used by Boyer, Ferguson-Smith & Grumbach (1961) in their study of Turner's syndrome. By this approach the parental ages at the birth of an achondroplasic were compared with their ages at the birth of the normal sibs in each sibship.

If the parental ages at the birth of the affected child were compared with the mean parental ages at the birth of normal sibs, the ages at the achondroplasic's birth were greater than the mean in 60 of 91 sibships and equal in 1. This simple sign test is significant at the 1 % level. This procedure, however, did not differentiate between the effects of parental age and birth order.

If all the sibships were considered together, the parental ages at the birth of the 91 achondroplasics for whom sib data were available were: fathers, 36·09 years, S.D. 7·49; mothers, 30·69 years, S.D. 5·97.

The mean parental ages at the birth of a total of 318 unaffected sibs were: fathers, 33·38 years, S.D. 7·49; mothers, 27·81 years, S.D. 6·49.

It was concluded from the results of these first two methods that there was a significant parental age effect on the occurrence of new achondroplasia mutations, but neither method separated the maternal and paternal components of this age effect.

These components were evaluated individually by a third approach, that outlined by Penrose (1957) using total and partial correlations. This method entails the calculation of six correlation

values which are then used to derive partial correlation coefficients that allow the independent effect of each variable to be studied when the other variables are held constant.

The first three of the six primary correlation values are ordinary product moment correlations as follows: (1) mother's age *v.* birth order, r_{mb} (Table 2); (2) father's age *v.* birth order, r_{fb}; (3) father's age *v.* mother's age, r_{fm} (Table 3). The remaining three values are point biserial coefficients of correlation for the following: (4) father's age *v.* incidence, r_{fi} (Table 4); (5) mother's age *v.* incidence, r_{mi} (Table 5); (6) birth order *v.* incidence, r_{bi} (Table 6). These latter three values are calculated by the formula analogous to the product moment correlations but appropriate for data with 0, 1 measurements on one of the characteristics.

Table 2. *Correlation table of mother's age and order of birth—United States* 1955 (*in thousands*)

Mother's Age	Order of birth 1	2	3	4	5	6	7	8	9	10	11	12	13	Totals
17	273·2	79·4	13·6	1·8	0·2	—	—	—	—	—	—	—	—	368·2
22	423·5	375·9	175·8	60·7	17·8	4·5	1·0	0·2	0·1	—	—	—	—	1059·5
27	173·0	295·3	245·4	129·1	58·4	25·7	10·5	4·0	1·4	0·5	0·1	0·1	—	943·5
32	63·0	136·2	162·9	111·8	61·4	33·5	18·8	10·6	5·8	2·9	1·3	0·6	0·2	609·0
37	23·2	46·8	63·4	53·7	35·5	22·4	14·6	10·1	7·1	4·9	2·9	1·7	1·0	287·3
42	5·2	8·6	12·0	11·4	9·4	6·8	4·9	3·8	2·9	2·5	1·9	1·5	1·0	71·9
47	0·3	0·3	0·5	0·5	0·4	0·4	0·3	0·3	0·3	0·2	0·2	0·2	0·1	4·0
Totals	961·4	942·5	673·6	369·0	183·1	93·3	50·1	29·0	17·6	11·0	6·4	4·1	2·3	3343·4

Mean birth order 2·64, S.D. 1·73. Mean age of mothers 26·43, S.D. 6·09. Correlation (r_{mb}) = +0·52.

Table 3. *Correlation table for father's age and mother's age* 1955 *figures for U.S. whites* (*in thousands*)

Mother's Age	Father's age 17	22	27	32	37	42	47	52	57	Totals
17	66·4	217·6	56·9	9·1	2·3	0·7	0·3	0·1	0·1	353·1
22	10·0	449·3	477·7	102·4	21·9	6·4	2·1	0·8	0·5	1071·1
27	0·3	39·9	455·9	352·4	88·1	21·9	6·6	2·2	1·3	968·6
32	0·0	3·2	53·3	290·7	199·3	58·2	15·5	4·9	2·5	627·6
37	0·0	0·4	5·6	33·5	129·7	89·4	27·1	7·5	3·7	296·9
42	0·0	0·1	0·5	2·3	10·2	32·0	20·4	6·3	2·9	74·7
47	0·0	0·0	0·0	0·0	0·2	0·6	1·9	0·9	0·4	4·0
Totals	76·7	710·1	1049·9	790·4	451·7	209·2	73·9	22·7	11·4	3396·0

Mean age of fathers 29·85, S.D. 6·95. Mean age of mothers 26·54, S.D. 6·07. Correlation (r_{fm}) = +0·76.

The Tables were constructed using data from the present study and U.S. Vital Statistics for 1955. For value 2(r_{fb}) the correlation used was that reported by Blank (1960) from birth data gathered at University College Hospital, London, as no comparable U.S. data were available.

The calculated correlation values were: (1) r_{mb} = +0·52, (2) r_{fb} = +0·30, (3) r_{fm} = +0·76, (4) r_{fi} = +0·41, (5) r_{mi} = +0·33, (6) r_{bi} = +0·20. From these r values the following second-order partial correlation coefficients were calculated: (7) the partial correlation for father's age *v.* incidence when mother's age and birth order are held constant, $r_{fi.\,mb}$ = +0·27; (8) the partial

Table 4. *Distribution of observed cases of achondroplasia according to father's age*

(Expected numbers based on U.S. data, 1955.)

Father's age	Observed	Expected	Obs./exp.
17	0	2·30	0·00
22	6	21·33	0·28
27	14	31·53	0·44
32	25	23·74	1·05
37	18	13·57	1·33
42	24	6·28	3·82
47	11	2·22	4·95
52	4	0·68	5·88
57	0	0·34	0·00
Total	102	101·99	
Mean	36·36	29·85	
S.D.	12·95	13·06	

Point biserial coefficient of correlation (r_{fi}) = +0·41.

Table 5. *Distribution of observed cases of achondroplasia according to mother's age*

(Expected numbers based on U.S. data, 1955.)

Mother's age	Observed	Expected	Obs./exp.
17	2	10·61	0·19
22	17	32·17	0·53
27	21	29·09	0·72
32	31	18·85	1·64
37	25	8·92	2·80
42	6	2·24	2·68
47	0	0·12	0·00
Total	102	102·00	
Mean	30·82	26·53	
S.D.	6·10	6·10	

Point biserial coefficient of correlation (r_{mi}) = +0·33.

Table 6. *Distribution of observed cases of achondroplasia according to birth order*

(Expected numbers based on U.S. data, 1955.)

Birth order	Observed	Expected	Obs./exp.
1	17	29·33	0·58
2	26	28·75	0·90
3	24	20·55	1·17
4	9	11·26	0·80
5	7	5·59	1·25
6	8	2·85	2·81
7	3	1·53	1·96
8	3	0·88	3·41
9	3	0·54	5·56
10	1	0·34	0·29
11	0	0·20	0·00
12	0	0·13	0·00
13	1	0·07	14·29
Total	102	102·02	
Mean	3·48	2·64	
S.D.	2·35	1·93	

Point biserial coefficient of correlation (r_{bi}) = +0·20.

correlation for mother's age and incidence when father's age and birth order are held constant, $r_{mi.fb} = -0{\cdot}01$; (9) the partial correlation for birth order *v.* incidence when father's and mother's ages are held constant, $r_{bi.fm} = +0{\cdot}09$.

As can be seen from values (7), (8) and (9), the only significant partial correlation coefficient for any variable *v.* incidence when the remaining two variables are held constant is 7, $r_{fi.mb}$. Thus, when mother's age and birth order are held constant, there remains a significant partial correlation between father's age and incidence ($P < 0{\cdot}01$).

This method successfully separated the maternal and paternal components of the significant parental age effect and showed that paternal age is the major factor in determining the occurrence of new mutations for achondroplasia.

Family data

The partners in 57 marriages involving achondroplasic dwarfs are presented in Table 7. Both partners were achondroplasic in 23 of these, while the remaining 34 involved either an individual with another type of dwarfism or a normal person. Since most of this information was obtained from members of the LPA the results are biased in favour of multiple dwarfs in a single family as a married achondroplasic is more likely to belong to the LPA if he or she has a dwarfed mate or affected relative. Several of the couples have yet to complete their families but many are beyond childbearing years.

Table 7. *Partners in marriages of achondroplasics* (57 *marriages*)

	Female		
Male	Achondroplasic	Non-achondroplasic dwarf	Normal
Achondroplasic	23	9	7
Non-achondroplasic dwarf	8	—	—
Normal	10	—	—

DISCUSSION

Some important facts about achondroplasia emerge from the statistics tabulated in the results section. The adult height and weight of an achondroplasic should be of value in answering the questions of parents about the growth expectation of their affected child. The data on parental age effects and on marriages of achondroplasics will be of general genetic interest and the latter may be of value in genetic counselling of affected individuals.

Both the sporadic and familial achondroplasic offspring of normal mothers weighed only slightly less than normal new-born infants. Birth weights averaged 7·69 lb. for affected males and 6·90 lb. for affected females, while normal males weigh 7·5 lb. (50th percentile) and females 7·4 lb. These normal birth weights may reflect the fact that most of individuals studied had already survived the first few years of life, so some achondroplasics of low birth weight who died in infancy may have been omitted.

In contrast to this group of achondroplasics, those with dwarfed mothers had much lower mean birth weights (6·51 lb. for males and 5·99 lb. for females). These values reflect the higher frequency of premature deliveries, the majority being Caesarean sections. These are done not only because the mother has a small pelvis but also because the affected infant has a large head.

In comparison to the nearly normal birth weights for affected infants with normal mothers, the birth lengths are below the 10th percentile for both males and females. The achondroplasic males averaged 18·84 in. in length *v.* a normal length of 19·9 in. (50th percentile) and the 10th percentile length of 18·9 in. Comparable figures for females were 18·55 in. for achondroplasics *v.* 19·8 in. (50th percentile) and 18·8 in. (10th percentile).

The adult height for affected males was 51·81 in. and for adult females, 48·62 in. Mørch (1941) reported comparable figures of 51·25 and 45·25 in. Most achondroplasics have heights similar to other affected individuals of the same sex, whatever the parental heights. Thus all male achondroplasics are much the same height. The picture is similar for females. In this situation the parental heights have little influence on the adult height of their sporadic achondroplasic child, in contrast to the usual relationship which a normal child's height bears to that of his parents. It would appear that the gene for achondroplasia so severely affects the growth plate that the usual genes determining height have little influence on the final outcome, although the normal effect of the individual's sex is manifest, with males being taller than females. This similarity in height is in accord with the remarkably constant phenotypic picture for the other aspects of achondroplasic dwarfism.

The mean adult weight for all achondroplasics was 110·24 lb. (120·61 lb. for males, 100·62 lb. for females). This compares with Mørch's mean of 110 lb. Obesity is a problem for many achondroplasics. Number 28 in our series was 54½ in. tall and weighed 287 lb. As can be seen from the weights listed in the Appendices there were a number of obese individuals. The relatively large trunk in relation to the short extremities may lay the foundation for obesity while lack of exercise helps to perpetuate it.

The parental age effect on the occurrence of new mutations for the achondroplasia gene has been discussed by Penrose (1961). He summarized the excess of the observed parental mean ages over control means for studies by Mørch (1941), Krooth (1952), Grebe (1955) and Stevenson (1957). This excess for father's ages ranged from 4·3 (Grebe) to 7·2 years (Stevenson), and for mothers 3·1 (Grebe) to 5·7 years (Krooth). The excesses found in the present study, 6·2 years for fathers' ages and 4·0 years for mothers', fall within the ranges of these four studies. An earlier study by Bleyer (1939) lists maternal ages of 303 achondroplasics from which a mean age of 29·16 years, S.D. 6·46, can be calculated. This compares with our mean of 30·52. He did not list paternal ages.

The three methods outlined in the results section all showed a significant parental age effect but only the method of partial correlations separated the paternal and maternal components. Computation of partial correlations on the present data shows no significant maternal age effect and thus supports Penrose's contention that the elevated maternal ages found in all studies is only a reflexion of the increased paternal age (Penrose, 1961). This elevated age of fathers at the birth of a sporadic achondroplasic is thought to be the major causal factor for the new mutation. The same phenomenon has been reported for Apert's acrocephalosyndactyly (Blank, 1960), the Marfan syndrome (Lynas, 1958) and fibrodysplasia ossificans progressiva (Tünte, Becker & von Knorre, 1967). The increased mutation rate with older fathers has been attributed to cumulative exposure to (*a*) natural ionizing radiation, (*b*) chemical mutagens, either exogenous or endogenous, through accumulation of toxic metabolic by-products, (*c*) or to an error in gene copying in spermatogenesis. These possibilities have been discussed by Penrose (1955). The differing time-tables for oogenesis and spermatogenesis account for the maternal age effect for

some chromosomal abnormalities and the paternal age effect for point mutations. In the model of spermatogenesis described by Clermont (1966), the pool of stem cell spermatogonia is constantly replenished by cell divisions producing equal numbers of the primitive stem cells and the more differentiated cells which proceed to mature spermatocytes. This continuing division of the stem cells may explain the progressive accumulation of mutant genes with age as copying errors are perpetuated. In contrast, the primitive oocytes formed in foetal life lie dormant until the initiation of oogenesis prior to ovulation. Thus these cells are not subject to the repeated divisions as are the spermatogonia.

The elevated birth order mean of 3·48 *v.* control of 2·64 also reflects the increased paternal age as no partial correlation between birth order and incidence is seen.

Through the LPA many dwarfs are able to make social contacts that lead to marriage to another person with short stature. Tables 7 and 8 summarize the marriages in this study. Mørch believed that 80% of achondroplasics did not survive the first year of life, although his information was based on a small number of infant achondroplasics and even this group may have included other chondrodystrophies. Potter (1961) reported that of 8 achondroplasic infants born in 100,000 deliveries at Chicago Lying-In Hospital only one survived early infancy. This was a familial case with both parents affected. The others were all sporadic.

Table 8. *The offspring of achondroplasics' marriages*

Marriage partners	Number of marriages	Fertile marriages	Children: Achondroplasic: Died in infancy	Children: Achondroplasic: Living	Children: Non-achondroplasic: Dwarfed	Children: Non-achondroplasic: Normal	Total children	Miscarriages
Achondroplasic × achondroplasic	23	14	7	9	—	7	23	3
Male achondroplasic × female normal	7	4	0	6	—	3	9	0
Female achondroplasic × male normal	10	9	0	10	—	1	11	1
Totals for achondroplasics × normals	17	13	0	16	—	4	20	1
Male achondroplasic × female non-achondroplasic dwarf	9	6	0	4	2	0	6	1
Female achondroplasic × male non-achondroplasic dwarf	8	4	0	4	0	1	5	1
Totals for achondroplasics × non-achondroplasic dwarfs	17	10	0	8	2	1	11	2
Totals for achondroplasics × non-achondroplasics	34	23	0	24	2	5	31	3

Our study suggests that the outlook for survival of the achondroplasic child may not be as bleak as previous reports would indicate. The nature of this study was such that fatal sporadic cases would be missed. A total of 40 familial cases were ascertained and are listed in Table 8.

All 24 affected children with only one affected parent, and therefore heterozygous, survived infancy. These children were heterozygous for the achondroplasia gene. The picture changes when the 16 children of two achondroplasics are considered, as 7 of these died in infancy. Since the children of two achondroplasics would be expected to conform to the 1:2:1 ratio of homozygous affected:heterozygous affected:normal, it is probable that some of these 7 affected individuals who died were homozygous for the achondroplasia gene. The same may be true for the three miscarriages in this group.

The phenotype of what is believed to be the homozygous achondroplasic has recently been described by Hall *et al.* (1969), and differentiated from thanatophoric dwarfism by Langer *et al.* (1969). These infants usually die *in utero* or in the neonatal period with respiratory distress. Radiologic changes are more severe than those seen in the heterozygous affected individual and even show some qualitative differences.

If only one marriage partner is an achondroplasic, equal numbers of achondroplasic and non-achondroplasic infants would be expected. Of the 31 children of such pairs only 7 were non-achondroplasics (Table 8). This can only be explained by a bias of ascertainment in that achondroplasics with normal children will be less likely to join the LPA than individuals with affected children.

The data presented suggest decreased fertility in achondroplasics if their marriages are compared with the general population. In 1955 only 16 % of women in the United States, 45–49 years of age, had not had children (U.S. Census), while 60 % of female achondroplasics who had reached this age were childless. If the marriages tabulated in Table 8 are considered one finds that 35 % of these are without offspring. Furthermore the fertile marriages produced only 1·4 children per family, which is smaller than the national average of 3·5 children per family (U.S. Census). The number of children when all achondroplasic marriages, fertile or not, are considered is only 0·96 children per marriage. The lowest reproductive rate of all was seen in marriages of achondroplasics with dwarfs of other types, where an average of only 0·65 children per marriage resulted. Many reasons can be given for this reduced fertility. Not the least of these is the desire of affected persons to limit the number of their children. A number of those who do want children choose to adopt dwarfed children. Female achondroplasics have the added difficulty of delivery, and neonatal mortality is increased because of the necessity of Caesarean section, superimposed upon the already handicapped affected child.

In the series of sporadic achondroplasics there were three sets of twins. Cases 62 and 63 were affected brothers. Case 21, an affected female, had a normal twin brother and case 34, also a female, had an affected sister. Zellweger & Taylor (1955) reported a pair of affected twin sisters and reviewed the literature to that date, finding 18 previously reported twin pairs. Half of these sets had both members affected and in half only one was affected. Of the twin pairs with both members affected two sets were discordant for sex. Unless one of the parents of each of these sets was affected it is difficult to accept these as true achondroplasics. The affected twins reported in this study, numbers 62 and 63, had identical adult heights and weights.

Although it is impossible to make an accurate evaluation of ethnicity, certain nationalities were mentioned frequently when achondroplasics were asked about their parental background. Northern European groups were the most commonly reported, either alone or in combination with others. English, alone or in combination with other nationalities, was given for 28 mothers and 30 fathers, Irish for 23 mothers and 25 fathers, German 18 mothers and 15 fathers, Dutch

11 mothers and 7 fathers, and Scottish 7 mothers and 9 fathers. French, Italian, Jewish, Polish and Negro were mentioned from 3 to 7 times. Many others, including the Scandinavian countries, Armenian and American Indian were reported 3 times or less. A total of 23 nationalities was obtained, although many of these made up a minor portion of the ethnic background of any individual. The ethnic background may reflect the composition of the LPA or could be associated with the later marriages of males of some ethnic groups with a resulting greater paternal age, particularly if the sibship is large.

SUMMARY

Statistics have been tabulated on 148 achondroplasics, of whom 117 (58 males and 59 females) were sporadic and 31 (15 males and 16 females) were familial cases.

1. Mean birth weights for achondroplasics with normal mothers were 7·69 lb. for males and 6·90 lb. for females. Mean birth weights for affected individuals with mothers who had achondroplasia or some other type of dwarfism were 6·51 lb. (males) and 5·99 lb. (females).

2. Mean birth lengths were 18·84 in. (males) and 18·55 in. (females) for achondroplasics with normal mothers and 17·95 in. (males) and 18·00 in. (females) for the offspring of dwarfed mothers.

3. Mean adult heights for achondroplasics were 51·81 in. (males) and 48·62 in. (females).

4. Mean adult weights were 120·61 lb. (males) and 100·62 lb. (females).

5. The parental heights did not significantly influence the adult height of the sporadic achondroplasic.

6. There was a significant parental age effect on the occurrence of new mutations for the achondroplasia gene. The paternal component of this parental age effect was the major factor in the occurence of such mutations. The increased maternal age and birth order was only a reflection of this elevated paternal age.

7. The outcome of 57 marriages involving achondroplasics was presented. The marriage partner was another achondroplasic in 23 marriages, an individual with another form of dwarfism in 17 and a normal person in 17. Only 37 of the 57 marriages were fertile.

8. The outlook for the survival of the heterozygous achondroplasic infant was not as bleak as had previously been thought. The 24 affected children who had only one achondroplasic parent all survived infancy. Of the 16 affected offspring of marriages in which both partners were achondroplasics, 7 died in infancy. It was probable that the majority of these cases were homozygous for the achondroplasia gene.

9. Achondroplasics had decreased fertility.

10. Presumed monozygotic male twins and two non-identical twin pairs with only one member affected were included in this study.

11. Ethnic differences in achondroplasia may be associated with the late marriages of the males of some races.

This work was supported by a grant from the National Foundation—March of Dimes.

REFERENCES

BLANK, C. E. (1960). Apert's syndrome (a type of acrocephalosyndactyly)—observations on a British series of thirty-nine cases. *Ann. Hum. Genet., Lond.* **24**, 151.

BLEYER, A. (1939). Role of advancing maternal age in causing achondroplasia. *Am. J. Dis. Child.* **58**, 994.

BOYER, S. H., FERGUSON-SMITH, M. A. & GRUMBACH, M. M. (1961). The lack of influence of parental age and birth order in the aetiology of nuclear sex chromatin-negative Turner's syndrome. *Ann. Hum. Genet., Lond.* **25**, 215.

CLERMONT, Y. (1966). Renewal of spermatogonia in man. *Am. J. Anat.* **118**, 509.

DENNIS, J. P., ROSENBERG, H. S. & ALVORD, E. C. (1961). Megalencephaly, internal hydrocephalus and other neurological aspects of achondroplasia. *Brain* **84**, 427.

GREBE, H. (1955). Chondrodysplasie. *Ed. dell'Istituto Gregorio Mendel, Roma.* Ref. Penrose (1961).

HALL, J. G., DORST, J. P., TAYBI, H., LANGER, L. O., SCOTT, C. I. & MCKUSICK, V. A. (1969). Two possible cases of homozygosity for the achondroplasia gene. *Proc. 1st Conf. Clin. Delin. Birth Defects*, Baltimore, Md., May, 1968. New York: National Foundation—March of Dimes. (In the Press.)

KROOTH, R. S. (1952). The aetiology of human malformations with special reference to congenital heart disease and achondroplasia. Ph.D. thesis, University of London. Ref. Penrose (1961).

LANGER, L. O., BAUMANN, P. A. & GORLIN, R. J. (1967). Achondroplasia. *Am. J. Roent. Rad. Ther. Nucl. Med.* **100**, 12.

LANGER, L. O., SPRANGER, J. W., GRIENACHER, I. & HERDMAN, R. C. (1969). Thanatophoric dwarfism. *Radiology* **92**, 285

LYNAS, M. A. (1958). Marfan's syndrome in Northern Ireland: an account of thirteen families. *Ann. Hum. Genet., Lond.* **22**, 289.

MARIE, P. (1900). L'achondroplasie dans l'adolescence et l'âge adulte. *Press. Med.* **8**, 17.

MØRCH, E. T. (1941). Chondrodystrophic dwarfs in Denmark. *Op. Domo Biol. hered. hum., Kbh.* **3**.

PARROT, J. M. (1878). Sur les malformations achondroplasiques et le dieu Ptah. *Bull. Soc. d'Antropol., Paris* **1**, 296.

PENROSE, L. S. (1955). Parental age and mutation. *Lancet* ii, 312.

PENROSE, L. S. (1957). Parental age in achondroplasia and mongolism. *Amer. J. Hum. Genet.* **9**, 167.

PENROSE, L. S. (1961). *Recent Advances in Human Genetics.* Boston: Little, Brown and Co.

POTTER, E. L. & COVERSTONE, V. (1948). Chondrodystrophy fetalis. *Am. J. Obst. Gyn.* **65**, 790.

POTTER, E. L. (1961). *Pathology of the Fetus and Newborn*, p. 163. Chicago: Year Book Medical Publishers Inc.

RUBIN, P. (1964). *Dynamic Classification of Bone Dysplasias*, p. 181. Chicago: Year Book Medical Publishers Inc.

SILVERMAN, F. N. & BRUNNER, S. (1967). Errors in the diagnosis of achondroplasia. *Acta Radiol (Diag.)* **6**, 305.

SLATIS, H. M. (1955). Comments on the rate of mutation to chondrodystrophy in man. *Am. J. Hum. Genet.* **7**, 76.

STEVENSON, A. C. (1957). Achondroplasia: an account of the condition in Northern Ireland. *Am. J. Hum. Genet.* **9**, 81.

TÜNTE, W., BECKER, P. E. & VON KNORRE, G. (1967). Zur genetik der myositis ossificans progressiva. *Humangenetik* **4**, 320.

VOGL, A. (1962). The fate of the achondroplastic dwarf (neurologic complications of achondroplasia). *Expl. Med. Surg.* **20**, 108.

ZELLWEGER, H. & TAYLOR, B. (1965). Genetic aspects of achondroplasia. *Journal-Lancet* **85**, 8.

Appendix 1. *Data relating to achondroplasic subject presumed to be due to new mutations*

Patient no.	Sex	Date of birth	Height (in.)	Weight (lb.)	Birth weight lb.	Birth weight oz.	Birth length (in.)	Birth rank	Unaffected sibs M	Unaffected sibs F	Unaffected sibs T	Age (years of parents*) Father	Age (years of parents*) Mother	Height of parents (in.) Father	Height of parents (in.) Mother	Notes
1	F	18. xi. 47	47	65	8	6	—	3	2	1	3	31	26	72	68	—
2	F	27. vi. 65	28½	26	5	8	18½	1	1	—	1	31	31	69	65	—
3	F	11. vii. 33	48	81	5	8	17½	1	1	—	1	34	31	71	59	—
4	M	9. iv. 30	57	100	5	13	—	1	2	—	2	28	28	72	67	Married to diastrophic dwarf. No children
5	M	30. viii. 06	50	125	6	12	14	3	3	2	5	32	31	72	64	Married to normal female. No children
6	F	28. x. 28	50	99	7	2	—	1	—	—	2	43	23	68	66	Married to male with Ellis–van Creveld syndrome. No children.
7	M	28. v. 22	50	128	10	0	20	1	3	1	4	34	23	68	64	Married to achondroplasic (8). One normal M child
8	F	9. ix. 32	50	93	9	12	—	6	4	2	6	—	35	72	63	Married to achondroplasic (7)
9	F	9. iii. 52	51	102	6	11	18	3	1	2	3	37	30	73	65	
10	F	9. ix. 15	50	93	7	4	—	8	5	3	8	47	37	69	68	Married to ateliotic dwarf. No children
11	F	13. vii. 13	48	120	4	8	—	—	—	—	—	24	22	66	64	Negro. Married to normal male. One achondroplasic F. child (127)
12	F	29. iv. 41	47	100	7	0	20	2	—	3	3	32	29	63	60	
13	F	20. iv. 43	50	95	5	0	17	4	2	1	3	43	40	69	63	Married twice: (*a*) normal male—1 M achond. child (131), (*b*) hypochondroplasic—1 F achond. child (130)
14	M	1911	49	128	—	—	—	13	—	—	15	50	40	—	—	Married to normal male. 1 F achond. child (139). Parents normal. Exact height unknown
15	F	15. vi. 37	46	90	6	13	19	3	3	1	4	31	25	68	64	Married to normal male. 1 normal child, 1 M achond. child (141)
16	M	24. ix. 21	55	150	10	—	—	2	1	—	1	51	26	72	65	Also has 5 half sibs, all normal
17	F	30. iv. 26	49	78	—	—	—	4	2	1	3	42	41	70	68	Married to achond. (18). Children: 1 M normal; 1 achond. (143). 2 achonds died in neonatal period with respiratory distress
18	M	11. iv. 20	53	130	7	—	20	9	3	6	9	49	35	64	62	Married to achond. (17)
19	F	17. v. 18	50	124	8	—	—	2	—	1	1	49	28	72	62	Also has 1 maternal half sib—normal
20	F	14. viii. 45	50	100	5	13	—	1	1	—	1	26	21	64	60	Married to achond. (56). No offspring
21	F	31. iii. 49	50	98	6	10	19	3	3	1	4	32	33	68	67	Has normal twin brother (73 in. tall)
22	F	18. ii. 27	50	90	—	—	—	—	—	—	9	—	—	—	—	Married to normal male. 1 F achond. child (122)
23	M	31. x. 67	25	—	7	14	19½	2	—	1	1	28	26	74	67	—
24	F	15. vi. 23	52	100	—	—	—	2	1	—	1	34	32	63	62	—
25	M	18. v. 65	27	20	7	—	18	5	3	1	4	36	30	69	63½	—
26	M	13. vii. 54	46	80	8	10	19	4	2	1	3	37	31	69½	61	Hydrocephalus
27	F	16. ii. 18	47	112	—	—	—	3	1	1	2	—	27	—	—	Married twice: (*a*) normal male—1 achond. child; (*b*) achond. (60)—no offspring. Also has 4 maternal half sibs—all normal
28	M	26. xi. 18	54½	287	9	8	—	3	2	1	3	36	22	66	66	Deceased
29	M	4. vi. 44	53	120	8	9	21	10	4	5	9	43	41	70	60	—
30	M	16. ii. 53	—	—	7	3	18	1	3	1	4	21	20	74	63	—
31	F	26. vi. 49	53	88	6	7	19	1	—	3	3	27	22	72	61	—
32	F	14. ii. 47	48	120	7	2	19	2	2	—	2	—	—	—	—	Married to achond. (33). No offspring

* At birth of subject.

Appendix 1. *Continued*

Patient no.	Sex	Date of birth	Height (in.)	Weight (lb.)	Birth weight lb.	Birth weight oz.	Birth length (in.)	Birth rank	Unaffected sibs M	Unaffected sibs F	Unaffected sibs T	Age (years) of parents* Father	Age (years) of parents* Mother	Height of parents (in.) Father	Height of parents (in.) Mother	Notes
33	M	26. xii. 47	51	95	10	12	—	6	1	4	5	46	34	70	63	Married to achond. (32). No offspring
34	F	27. v. 55	51	—	5	8	—	2	1	2	3	27	—	71	63	Patient has normal twin sister
35	F	12. i. 01	47	122	—	—	—	5	—	4	4	40	37	67	64	Married normal male. No offspring
36	F	*20. vi. 25*	*50*	*93*	—	—	—	—	—	—	—	—	—	—	—	—
37	F	11. vi. 27	50	94	6	8	19	3	1	1	2	31	33	67	67	Married achond. (68). 1 normal child
38	M	1. vi. 67	—	—	8	3	19	7	4	2	6	40	38	70	62	—
39	M	10. viii. 56	44½	70	6	3	18	2	2	1	3	22	23	68	63½	—
40	F	10. v. 26	49	105	8	8	19	2	1	2	3	30	28	70½	63	Married achond. (120). 1 normal child
41	F	16. viii. 39	49½	97	9	8	20	3	1	1	2	39	30	67	65½	Married to pseudo-achondroplasic spondylo-epiphyseal dysplasia. 1 M achond. child (123). 1 F achond. child (124). No normal children
42	M	21. iv. 27	52	134	—	—	—	1	—	1	1	33	25	72	66	Married achond. (43)
43	F	21. xii. 30	52	138	—	—	—	6	2	3	5	37	35	65	66	Married achond. (44). Offspring: 4 achond. (125, 126). 1 F died at 2 days and 1 M at 3 months
44	M	1. i. 41	54	138	6	8	18½	2	—	—	5	34	22	71	67	Married achond. (128). No offspring
45	M	22. iii. 31	49	140	4	5	19	4	—	1	1	31	31	69	65	Married to diastrophic dwarf—1 F achond. (129). Patient has 3 maternal half sibs—all normal
46	M	5. i. 18	55	105	7	—	19	2	4	3	7	23	17	74	68	Married achond. (47)
47	F	20. iv. 22	50	100	6	—	18½	8	6	2	8	43	38	67	68	Married achond. (46). 1 normal child. 1 M achond. (132)
48	M	14. ix. 32	53	148	9	—	—	7	2	4	6	41	39	73	62	Married to normal female. Children: 1 M achond. (133). 1 F achond. (134)
49	M	23. iii. 21	55½	—	9	—	19½	2	—	3	3	28	25	70½	64	Married to achond. (137). Children: 1 F achond. (128). 1 M achond. (138)
50	F	15. xi. 42	45½	175	7	10	—	1	—	—	—	25	21	70	64½	Married achond. (51). 1 M achond. child (140)
51	M	26. v. 29	52½	105	—	—	—	9	5	4	9	42	36	—	—	Married achond. (50)
52	F	19. xi. 32	50	94	6	8	—	6	5	1	6	35	34	69	67	Married achond. (53). No offspring
53	M	1. ix. 33	54	140	—	—	—	6	5	2	7	32	29	66	65	Married achond. (52)
54	F	28. vi. 36	51½	100	7	—	—	2	1	—	1	33	29	64	63	Married achond. (55). 1 achond. child (142) dead
55	M	26. iv. 37	53	115	10	11	21	3	—	2	2	26	22	70	63	Married achond. (54)
56	M	13. ii. 40	51	103	—	—	—	2	—	1	1	25	22	72	69	Married achond. (20). No offspring
57	F	16. xi. 45	50	105	7	½	18¾	3	1	2	3	31	30	66½	63½	Married achond. (58). No children
58	M	30. i. 44	53½	130	8	—	18½	9	4	5	9	43	40	68½	60½	Married achond. (57)
59	M	28. ii. 18	48	110	8	—	—	4	2	1	3	28	29	70	65	Married to vit. D resistant rickets. No offspring. Patient has 2 maternal half sibs—normal
60	M	14. v. 15	52	114	—	—	—	7	2	4	6	48	37	—	—	Married achond. (27). No children
61	M	14. vi. 64	29½	23	8	7	19	2	—	2	2	30	29	72	66	—
62	M	15. vi. 18	49	110	5	12	—	5	4	—	4	51	37	74	69	Monozygotic twin of (63)
63	M	15. vi. 18	49	110	5	4	—	5	4	—	4	51	37	74	69	Monozygotic twin of (62)
64	M	13. vii. 47	53½	140	8	4	19	3	1	1	2	39	36	67	64	Married to pseudo-achondroplasic spondylo-epiphyseal dysplasia: 1 F achond. child (146)
65	M	8. viii. 42	51	130	—	—	—	3	1	1	2	42	33	66	63	Married to hypochondroplasic—1 hypochondroplasic child (F)
66	M	22. vii. 33	53	110	—	—	—	1	—	—	0	32	—	70	—	Married to panhypopituitary dwarf. No children

Appendix 1. *Continued*

Patient no.	Sex	Date of birth	Height (in.)	Weight (lb.)	Birth weight lb.	Birth weight oz.	Birth length (in.)	Birth rank	Unaffected sibs M	Unaffected sibs F	Unaffected sibs T	Age (years) of parents* Father	Age (years) of parents* Mother	Height of parents (in.) Father	Height of parents (in.) Mother	Notes
67	M	27. v. 20	51	120	6	11	—	2	1	—	1	48	31	60	60	Married to normal. 1 F achond. child (144). 1 M achond. child (145)
68	M	19. vi. 20	52	113	7	—	21	1	1	1	2	23	18	72	63	Married achond. (37). 1 normal child. Patient also has 1 maternal half sib—normal
69	M	15. viii. 03	51	110	8	—	18	8	4	4	8	45	40	69	68	Married to Turner's syndrome. No offspring
70	M	23. vii. 62	35½	32	5	—	18½	3	1	1	2	37	34	69½	62	—
71	M	29. x. 05	50	108	6	8	—	1	—	1	1	26	24	66	65	Married achond. (72)
72	F	17. iii. 13	49	108	5	4	—	5	5	4	9	31	32	67	65	Married achond. (71). No children
73	M	28. iv. 20	48	100	—	—	—	2	1	1	2	43	30	66	66	Married achond. (118). No children
74	M	26. xi. 34	52½	139	—	—	18	3	1	1	2	37	39	68	62	Married achond. (75)
75	F	20. ii. 31	48	108	8	8	18	1	—	1	1	41	29	—	64	Married achond. (74). 1 normal child
76	F	4. xii. 35	47	75	7	8	18½	5	2	2	4	45	36	74	69	Married to pseudo-achondroplasic spondylo-epiphyseal dysplasia. No children
77	F	6. vii. 37	44	89	—	—	—	3	1	2	3	37	39	65	62	—
78	F	18. x. 23	45	125	8	6	20	6	7	6	13	40	29	66	64	Married to normal. No children
79	F	8. x. 98	47	100	3	8	—	2	4	1	5	44	31	65	65	Married to achond. 1 F achond. child
80	F	7. v. 48	47	105	8	3	19	3	1	1	2	50	35	70	64	Has 1 normal half-sib
81	F	2. ix. 02	48	86	7	—	—	1	2	—	2	32	21	72	67	Married to achond. (82). 1 M achond. child (120). 1 F achond. (121)
82	M	28. xii. 00	52	130	7	—	—	—	6	—	6	46	31	74	72	Married to achond. (81)
83	M	17. x. 22	54	135	—	—	—	2	1	—	1	30	30	71	66	—
84	M	17. iv. 56	43	76	7	6	—	2	4	—	4	25	20	69	66	—
85	M	11. x. 49	50	75	7	12	20	2	1	—	1	—	—	—	—	—
86	M	16. vi. 42	52	110	7	9	18½	3	1	1	2	43	34	71	63	—
87	M	25. xi. 28	51	110	—	—	—	4	—	3	3	40	35	65	64	—
88	F	12. iv. 57	43	74	5	12	16½	2	3	2	5	27	25	70	62	—
89	F	26. iv. 35	48	105	6	5	19	3	4	—	4	44	26	70	67	Married to achond. (117). No offspring
90	F	4. xi. 66	24½	16	8	12	18	4	—	—	3	35	33	67	62	—
91	F	27. i. 12	42	85	—	—	—	4	5	3	8	30	20	66	65	—
92	F	4. viii. 44	46½	75	9	—	—	—	1	1	2	—	32	—	—	—
93	F	28. x. 63	30	24	—	—	—	5	3	2	5	39	33	70	67	—
94	F	15. v. 58	40	49	6	14	18	1	1	—	1	—	—	72	63¾	—
95	F	28. ii. 52	48	90	6	7	—	3	1	1	2	48	35	70	61	—
96	F	3. viii. 55	42	46	6	14	17	2	1	—	1	32	30	67½	64	—
97	F	5. xi. 47	44	90	6	8	19	3	—	2	2	36	35	63	63½	—
98	M	12. x. 43	54	118	—	—	18	4	1	2	3	44	37	68	63	—
99	M	11. xi. 36	52	130	7	8	17	2	—	1	1	38	35	71	66	—
100	M	26. xii. 47	50	95	10	12	—	6	1	4	5	45	34	70	63	—
101	F	27. iv. 60	35¾	35	7	6	18	2	1	—	1	28	27	69	65	—
102	M	7. xi. 08	48	111	—	—	—	—	—	—	—	—	—	—	—	—

* At birth of subject.

Appendix 1. *Continued*

Patient no.	Sex	Date of Birth	Height (in.)	Weight (lb.)	Birth weight lb.	Birth weight oz.	Birth length (in.)	Birth rank	Unaffected sibs M	Unaffected sibs F	Unaffected sibs T	Age (years) of parents* Father	Age (years) of parents* Mother	Height of parents (in.) Father	Height of parents (in.) Mother	Notes
103	F	8. xii. 44	48	87	6	11½	18½	3	1	1	2	34	30	71	66½	—
104	M	27. ix. 66	28	22	6	12	19	2	1	—	1	35	34	69	62	—
105	F	12. i. 01	47	122	—	—	—	5	—	4	4	41	37	66	64	—
106	F	21. xii. 46	52	110	8	4	20	1	—	—	0	37	33	72	67	Married normal. 2 achond. children. Has unaffected paternal half-sister
107	M	19. viii. 47	52	97	7	—	—	3	2	—	2	33	26	71	69	—
108	F	31. xii. 44	51	110	—	—	—	2	1	—	1	40	38	67	66	—
109	M	6. viii. 52	48	82	7	4	20½	2	1	1	2	42	37	73	65	—
110	F	18. v. 61	—	38	—	—	—	3	2	1	3	44	36	71	62½	—
111	F	5. ii. 50	46	95	7	6	—	1	2	—	2	24	22	65	64	—
112	F	26. vii. 60	33	33	—	—	18	2	2	1	3	41	35	70	62	—
113	M	24. x. 12	53	136	—	—	—	2	1	—	1	—	—	71	70	Married normal—no children. Unaffected half-brother
114	F	29. x. 50	50	110	5	8	20	1	2	—	2	28	26	70½	69	—
115	M	11. iv. 97	48	70	10	—	—	6	4	3	7	38	30	72	64	Married vit. D resist. rickets—daughter with vitamin D resist. rickets
116	M	17. v. 54	47	75	6	—	18	—	—	—	—	—	—	—	—	—
117	M	16. x. 21	54	140	10	—	—	1	—	—	—	27	26	72	71	Married twice: (*a*) achond.—2 child.: 1 normal; 1 died in infancy—affected? (*b*) achond. (89)—no offspring

* *At birth of subject.*

Appendix 2. *Data relating to familial cases of achondroplasia*

Patient no.	Sex	Date of birth	Height (in.)	Weight (lb.)	Birth weight lb.	Birth weight oz.	Birth length (in.)	Sibs Normal	Sibs Affected	Sibs Total	Parents Father	Ht	Parents Mother	Ht	Notes
118	F	24. ii. 22	49	—	5	—	—	0	0	0	Dwarf	52	Achond.	47	Married to achond. (73). No children
119	M	5. xii. 33	54	115	—	—	—	0	0	0	Achond.	47	Normal	70	Married to vit. D resist. Rickets. 1 daughter—achond. (3rd generation)
120	M	5. vii. 25	50	102	7	8	17½	0	F (121)	1	Achond. (82)	52	Achond. (81)	48	Married to achond. (40). 1 normal child
121	F	18. iii. 32	48	90	6	6	17½	0	M (120)	1	Achond. (82)	—	Achond. (81)	—	—
122	F	9. ii. 53	50	—	5	12	19½	0	0	0	Achond. (22)	50	Normal	68	—
123	M	13. vi. 66	—	—	6	9	18	0	F (124)	1	Pseudo-achond. Spondylo-epiph. dysplasia	—	Achond. (41)	49½	—
124	F	1. vii. 64	—	—	6	5	19½	0	M (123)	1	Pseudo-acond. S.E.D.	—	Achond. (41)	—	—
125	M	23. i. 58	43½	62	6	4	17¾	0	2 M (126), 1 F	3	Achond. (42)	54	Achond. (43)	52	2 affected sibs died in infancy
126	M	5. ii. 57	45½	79	6	15	18½	0	2 M (125), 1 F	3	Achond. (42)	54	Achond. (43)	52	See (125)
127	F	29. ii. 36	51	103	5	0	15	0	0	0	Normal	—	Achond. (11)	48	—
128	F	11. xi. 44	52	117	8	5	19½	—	—	1	Dwarf	55	Dwarf	53	Married to achond. (44). No children
129	F	12. viii. 60	39	—	7	11½	19	0	0	0	Achond. (45)	49	Diastrophic	42	—
130	F	2. iii. 68	—	—	4	13	16½	0	0	0	Hypochond	50	Achond. (13)	50	1 mat. half-brother affected (131)
131	M	19. vi. 64	31½	27	6	3	17¾	0	0	0	Normal	68	Achond. (13)	50	1 mat. half-sister affected (130)
132	M	25. v. 48	53	120	5	14	18½	1	0	1	Achond. (46)	55	Achond. (47)	50	—
133	M	5. ii. 68	—	—	6	5	18	0	F (134)	1	Achond. (48)	52	Normal	59	—
134	F	4. v. 66	—	—	7	8	18½	0	M (133)	1	Achond. (48)	52	Normal	59	—
135	F	20. vi. 41	46	83	6	0	—	0	0	0	Normal	60	Achond. (148)	Under 60	Married to normal. 1 affected son (136) Negro
136	M	26. i. 65	—	—	7	8½	18	0	0	0	Normal	72	Achond. (135)	—	4th generation with achond.
137	F	3. iv. 24	53	110	5	0	—	0	0	0	Normal	75	Achond.	48	Married to achond. (49). 2 affected children Married (138) F. (128)
138	M	31. i. 50	56	120	6	5	18½	0	F (128)	1	Achond. (49)	55½	Achond. (137)	53	—
139	F	17. vii. 49	46	85	—	—	—	0	0	0	Achond. (14)	49	Normal	58	—
140	M	19. iv. 68	—	—	5	15	18	0	0	0	Achond. (51)	52½	Achond. (50)	45½	—

Appendix 2. *Continued*

Patient no.	Sex	Date of birth	Height (in.)	Weight (lb.)	Birth weight lb.	Birth weight oz.	Birth length (in.)	Sibs Normal	Sibs Affected	Sibs Total	Parents Father	Parents Ht	Parents Mother	Parents Ht	Notes
141	M	22. x. 62	—	—	6	1½	18	1	0	1	Normal	—	Achond. (15)	46	—
142	M	18. ii. 67	—	—	6	7	17	0	0	0	Achond. (55)	53	Achond. (54)	51½	Died in neonatal period
143	F	22. vii. 55	53	94	5	9½	19	M	M, F	3	Achond. (18)	53	Achond. (17)	49	Both affected sibs died within two days of birth with respiratory distress
144	F	13. ii. 54	47	—	6	4	16	F	M (145)	2	Achond. (67)	51	Normal	65½	—
145	M	3. v. 50	52	120	8	2	19½	F	F (144)	2	Achond. (67)	51	Normal	65½	—
146	F	18. xi. 68	—	—	5	12	18	0	0	0	Achond. (64)	53½	Pseudo-achond. S.E.D.	48	—
147	M	10. xi. 68	—	—	—	—	—	0	0	0	Isolated HGH deficiency	—	Achond.	45	—
148	F	4. iv. 23	<60	—	—	—	—	2 M	0	2	Achond.	Under 48	Normal	—	Married to normal (4th cousin); 1 affected daughter (135); grandmother of (136)